Surgery for Congenital Heart Disease

A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery

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Objective: This study was undertaken to evaluate the effect of triiodothyronine replacement on the early postoperative course of neonates undergoing aortic arch reconstruction.

Methods: We performed a randomized, double-blind, placebo-controlled trial of triiodothyronine supplementation in neonates undergoing either a Norwood procedure or two-ventricle repair of interrupted aortic arch and ventricular septal defect. Patients were assigned to receive a continuous infusion of triiodothyronine (0.05 μ/kg/h) or placebo for 72 hours after cardiopulmonary bypass. Primary end points were a composite clinical outcome score and cardiac index at 48 postoperative hours.

Results: We enrolled 42 patients (triiodothyronine n = 22, placebo n = 20). Baseline characteristics were similar in the treatment groups. Study drug was discontinued prematurely because of hypertension (n = 1) and ectopic atrial tachycardia (n = 1), both cases in the triiodothyronine group. Free and total triiodothyronine levels were higher in the triiodothyronine group than in the placebo group at 24, 48, and 72 postoperative hours ($P < .001$). The median clinical outcome scores were 2.0 (range 0-4) with triiodothyronine and 2.0 (range 0-7) with placebo ($P = .046$). Compared with those in the placebo group, neonates assigned to triiodothyronine had shorter median time to negative fluid balance (2.0 vs 2.5 days, $P = .027$). Cardiac index values were 2.11 ± 0.64 L/min $\cdot$ m^2 with triiodothyronine and 2.05 ± 0.72 L/min $\cdot$ m^2 with placebo ($P = .81$). Heart rate and diastolic blood pressure were not influenced by triiodothyronine supplementation, but systolic blood pressure was higher in the triiodothyronine group ($P < .001$). No serious adverse events were attributed to triiodothyronine administration.

Conclusion: Triiodothyronine supplementation was safe and resulted in more rapid achievement of negative fluid balance after aortic arch reconstruction. Cardiac index at 48 hours was not significantly improved.

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Supported by the Glaser Pediatric Research Network and grant RR002172 from the National Institutes of Health.

Received for publication March 5, 2005; revisions received April 20, 2005; accepted for publication April 28, 2005.

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J Thorac Cardiovasc Surg 2005;130:810-6

0022-5223/$30.00

doi:10.1016/j.jtcvs.2005.04.025

Low cardiac output syndrome is a common complication of neonatal cardiac surgery.[1] Contributing factors include myocardial ischemia during aortic crossclamping, the effects of cardioplegia, the inflammatory reaction to cardiopulmonary bypass (CPB), hypothermia, and reperfusion injury.[2] Low cardiac

TABLE 1. Composite clinical outcome score

Clinical variable	Score		
	0	1	2
Time until negative fluid balance first achieved (d)	≤3	4-5	≥6
Time until sternal closure (d)	≤2	3-4	≥5
Time until first extubation (d)	≤4	5-8	≥9

Each patient received a score between 0 and 6 by adding the individual scores for each clinical variable. A score of 7 was assigned to patients who died or required extracorporeal membrane oxygenation support. *d,* Days.

output in the postoperative patient continues to be a source of significant morbidity, sometimes warranting the use of mechanical circulatory support.[2] Hoffman and colleagues[3] demonstrated that the incidence of low cardiac output syndrome in children undergoing corrective cardiac procedures is reduced by high-dose milrinone, a phosphodiesterase inhibitor. Additional therapies that both support the myocardium and lower systemic vascular resistance after congenital heart surgery would be valuable in treating the neonates at highest risk.

Thyroid hormones have important effects on cardiovascular function.[4] These include an increase in cardiac contractility[5] and a lowering of systemic vascular resistance mediated by dilation of resistance arterioles in the peripheral circulation.[6] However, levels of triiodothyronine (T_3), the biologically active hormone in cardiac myocytes, are significantly depressed in infants and older children after CPB.[7,8] Low T_3 levels in the early postoperative period therefore may contribute to the evolution of low cardiac output syndrome. Previous studies have suggested that neonates and patients undergoing more lengthy procedures may benefit from T_3 replacement, with improved cardiac output and more favorable intensive care unit (ICU) acuity scores.[9,10]

The purpose of this study was to evaluate the effect of T_3 replacement on the early postoperative course in a homogeneous group of high-risk neonates undergoing either the Norwood procedure or repair of ventricular septal defect and interrupted aortic arch. Specifically, we tested the hypothesis that T_3 replacement plus conventional therapy would be associated with better early postoperative outcome than would placebo plus conventional therapy.

Methods

Study Participants

A patient satisfied the inclusion criteria if he or she was (1) a neonate who had a diagnosis of hypoplastic left heart syndrome or another functional single-ventricle lesion with aortic arch obstruction and was scheduled to undergo the Norwood procedure with either a modified Blalock-Taussig shunt or a right ventricle–to–pulmonary artery conduit or (2) a neonate who had ventricular septal defect and interrupted aortic arch and was scheduled to undergo two-ventricle repair. Patients were excluded if they had birth weight lower than 2.3 kg, preoperative tachyarrhythmia, clinical sepsis confirmed by culture, serum creatinine greater than 133 μmol/L (1.5 mg/dL) within 24 hours of surgery, or a known thyroid or metabolic disorder. Written, informed consent was required from the parents or legal guardians before randomization.

Study Design

The study had two phases. Phase 1 was an open-label, dose-finding phase. The first 5 patients received an infusion of T_3 (King Pharmaceuticals, Cary, NC) for 72 hours beginning at the completion of CPB at a dose of 0.0625 μg/kg/h); 2 subsequent patients received a dose of 0.05 μg/kg/h) on the basis of an analysis of serum T_3 levels in the initial 5 patients. Phase 2 was a randomized, double-blind, placebo-controlled, single-center study. Randomization was performed with a computer-based random-number generator in permuted blocks of 2 and 4 and was stratified by surgeon and surgical procedure (Norwood palliation or ventricular septal defect and interrupted aortic arch repair). Eligible patients whose parents consented to study participation were randomly assigned preoperatively to receive a 72-hour infusion of either T_3 (0.05 μg/kg/h) or placebo (0.9% sodium chloride solution). Vasoactive infusions and other routine postoperative care were administered at the discretion of the surgical and ICU teams. Levels of total and free T_3, total and free thyroxine (T_4), thyroid-stimulating hormone, and T_3 resin uptake were measured before initiation of CPB; at the end of CPB before starting study drug; at 24, 48, and 72 postoperative hours; and at 7 and 14 postoperative days. Total T_3 and T_4 concentrations were measured by competitive chemiluminescent immunoassay, free T_3 was measured by equilibrium tracer dialysis, and free T_4 was measured by direct dialysis. All specimens were analyzed at a core laboratory (Nichols Institute, San Juan Capistrano, Calif).

Surgical Techniques

Patients with a functional single ventricle and aortic arch obstruction underwent a Norwood procedure with a modified Blalock-Taussig shunt[11] or a right ventricle–to–pulmonary artery polytetrafluoroethylene conduit (Gore-Tex conduit; W. L. Gore & Associates, Inc, Flagstaff, Ariz)[12,13] at the discretion of the attending surgeon. Patients with interrupted aortic arch and two functional ventricles underwent complete repair as previously described.[14] A pH-stat perfusion strategy was used in all patients. Methylprednisolone (30 mg/kg) was administered at initiation of CPB, and deep hypothermic circulatory arrest was used routinely, during which core temperatures were lowered to 18°C. Continuous ultrafiltration was used as patients were being rewarmed and weaned from CPB.

TABLE 2. Patient characteristics

Patient characteristic	T_3 (n = 22)	Placebo (n = 20)	*P* value
Birth weight (kg)	3.3 ± 0.5	3.4 ± 0.6	.53
Body surface area (m^2)	0.22 ± 0.02	0.22 ± 0.03	.99
Male sex (No.)	13 (59%)	14 (70%)	.53
Gestational age (wk)	38.9 ± 1.9	38.4 ± 1.5	.40
Apgar score at 1 min	7.4 ± 1.5	7.0 ± 2.1	.41
Apgar score at 5 min	8.3 ± 1.2	8.4 ± 0.9	.84
Age at surgery (d)	7.1 ± 4.0	5.8 ± 2.9	.21
Diagnosis (No.)			
Hypoplastic left heart syndrome	17 (77%)	16 (80%)	>.999
Other single ventricle with arch obstruction	3 (14%)	2 (10%)	
Interrupted aortic arch	2 (9%)	2 (10%)	
Ethnicity (No.)			
White	20	18	.79
Black	2	1	
Other	0	1	
Prenatal cardiac diagnosis (No.)	8 (36%)	10 (50%)	.53
Preoperative serum creatinine (μmol/L)	46.0 ± 15.0	42.4 ± 18.6	.50
Preoperative serum lactate (mmol/L)	1.9 ± 1.0	1.8 ± 0.7	.80
Mechanically ventilated before surgery (%)	11 (50%)	13 (65%)	.37
Extubated before surgery* (No.)	2 (18%)	3 (23%)	>.999
Surgical procedure (No.)			
Norwood with aortopulmonary shunt	8 (36%)	8 (40%)	>.999
Norwood with right ventricle–pulmonary artery shunt	12 (55%)	10 (50%)	
Two-ventricle repair of interrupted aortic arch	2 (9%)	2 (10%)	
Duration of CPB (min)	111 ± 47	98 ± 32	.31
Duration of aortic crossclamping (min)	55 ± 24	63 ± 19	.25
Duration of circulatory arrest (min)	36 ± 19	50 ± 18	.014

Results are presented as mean ± SD as appropriate. *Percentage is with reference to patients mechanically ventilated before surgery.

Study End Points

The primary end points were as follows: (1) a composite clinical score created for the trial and (2) cardiac index (CI) measured at 48 postoperative hours. The composite clinical score, derived through consensus by experts in pediatric cardiac intensive care, consisted of variables that reflect the rate of early postoperative recovery (Table 1). Lower scores represented a more favorable postoperative course. CI was measured at 48 postoperative hours because the nadir in T_3 level has been shown to occur at this time in pediatric cardiac patients,[8] so we believed that we would be most likely to detect a difference between treatment groups at that point. CI was determined by simultaneously measuring oxygen consumption (Co_2) with a previously validated real-time gas-exchange technique,[15] hemoglobin (in grams per liter), venous oxygen saturation from the superior vena cava ($Ssvco_2$) and arterial oxygen saturation (Sao_2) by co-oximetry, and entering values into the following formula: $Qs = Co_2/[(Sao_2 - Ssvco_2) \times 1.36 \times \text{hemoglobin} \times 100]$, where *Qs* is the systemic cardiac output. Patients were sedated, paralyzed, and mechanically ventilated, and had a cuffed tracheal tube to prevent air leak so that the accuracy of Co_2 measurements could be optimized. The inspired fraction of oxygen was not higher than 0.40 at the time of these measurements.

Secondary end points included serum lactate levels at 12, 24, and 48 hours after the termination of CPB, incidence of serious adverse events (recorded until the time of hospital discharge), oxygen delivery (Do_2),[16] and the ratio Do_2/Co_2, which reflects the relative excess of Do_2.[17] Do_2 was calculated as the product of $Cao_2 \times Qs$, where $Cao_2 = 1.36 \times \text{hemoglobin} \times Sao_2 \times 100$. Inotrope score was determined for the initial 5 postoperative days, as modified from Wernovsky and coworkers.[1]

Serum cortisol was measured immediately before CPB and at 24 and 48 hours after the operation. Ionized calcium was measured at 12, 24, and 48 postoperative hours.

Patient Safety

Criteria for premature termination of the study drug infusion were as follows: (1) sinus tachycardia (>200 beats/min) lasting longer than 15 minutes, (2) high systolic blood pressure (>90 mm Hg) for longer than 15 minutes, or (3) any tachyarrhythmia lasting longer than 30 seconds. An external Data Safety and Monitoring Board was established to oversee the safety of study participants. The study was approved by the Committee on Clinical Investigation at Children's Hospital Boston.

Statistical Analysis

Sample-size calculations were based on the primary study end point of CI at 48 postoperative hours. Assuming that mean CI

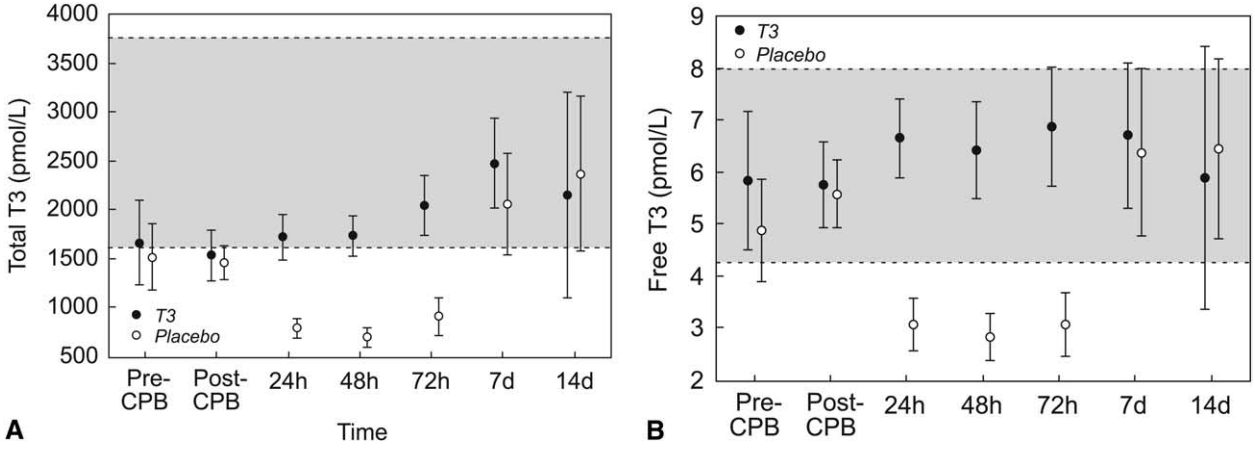

Figure 1. T_3 levels measured in the operating room before and after CPB and at 24, 48, and 72 postoperative hours and 7 and 14 postoperative days. *Error bars* represent 95% confidence intervals. *Shaded zones* indicate normal ranges (Nichols Institute, San Juan Capistrano, Calif). Total T_3 levels (A) and free T_3 levels (B) were higher in the T_3 group at 24, 48, and 72 postoperative hours ($P < .001$).

would be 2.0 L/min · m^2 with SD 0.5 L/min · m^2 in the placebo group, a sample size of 21 patients in each arm was required to detect a 25% increase in CI in the T_3 group, with a 2-tailed, 2-sample *t* test conducted at the .05 level with 90% power. Analyses were performed on an intent-to-treat basis. Comparisons of preoperative, intraoperative, and postoperative variables between treatment groups, including the primary and secondary outcome variables, were made with linear regression analysis or the Wilcoxon rank sum test for continuous variables, the Wilcoxon rank sum test for ordinal variables, and the Fisher exact test for categoric variables. Repeated measures analysis of variance was used for comparisons of serial measurements of heart rate, blood pressure, and thyroid function tests across time. Analyses were performed with Statistical Analysis Systems software, version 9 (SAS Institute, Inc, Cary, NC).

Results

Between July 2002 and April 2004, a total of 61 patients were eligible for study participation. Participation was declined by parents or guardians of 5 patients, and insufficient time to enroll before surgery prevented participation of an additional 6 patients. The remaining 50 patients were enrolled, 7 to the open-label phase and 43 to the randomized phase. A single patient was withdrawn from the randomized phase before initiation of study drug because extracorporeal membrane oxygenation support was required in the operating room after CPB. The remaining 42 patients (T_3 n = 22, placebo n = 20) form the study group for analysis. The patient who was withdrawn had been randomly assigned to the placebo arm; she eventually died and accounts for the only in-hospital death.

The first 5 patients of the open-label phase received a T_3 dose of 0.0625 μg/kg/h and had mean free T_3 levels of 7.3 $\pm$ 4.0 pmol/L at 24 postoperative hours, 8.7 $\pm$ 0.4 pmol/L at 48 hours, and 7.9 $\pm$ 2.4 pmol/L at 72 hours (normal range 4.3-8.0 pmol/L; Nichols Institute, San Juan Capistrano, Calif). The next 2 patients received a dose of 0.05 μg/kg/h) and had mean free T_3 levels of 6.0 pmol/L (24 hours), 7.7 pmol/L (48 hours), and 4.7 pmol/L (72 hours). The latter 2 patients formed the basis for a T_3 dose of 0.05 μg/kg/h in the randomized phase.

There were no statistically significant differences between the two treatment groups with respect to demographic variables, diagnosis, surgical procedure, or duration of CPB (Table 2). The proportion of patients who underwent Norwood procedures with a right ventricle–to–pulmonary artery conduit was comparable in the T_3 and placebo groups. The duration of deep hypothermic circulatory arrest was shorter in the T_3 group than in the placebo group (Table 2).

The study drug was stopped 2 hours prematurely in 1 patient because of mild, brief hypertension; the drug was stopped 33 hours prematurely in a second patient because of ectopic atrial tachycardia, which was transient (a 7-minute episode with a maximum heart rate of 231 beats/min) and hemodynamically well tolerated. The patient with ectopic atrial tachycardia had subsequent episodes of tachyarrhythmia as late as 6 days after termination of study drug. Both patients were in the T_3 arm. Neither patient had a serious adverse event. Temporary loss of peripheral venous access or lack of availability of study drug resulted in an interruption of study drug infusion in 3 patients in the T_3 arm and 1 patient in the placebo arm. No interruption lasted longer than 2 hours. All other patients received the study drug as intended.

Total and free T_3 levels were significantly higher in the T_3 group than in the placebo group at 24, 48, and 72

TABLE 3. Results of the composite clinical outcome score

Outcome	T_3 (n = 22)	Placebo (n = 20)	*P* value
Composite clinical score	2.0 (0-4)	2.0 (0-7)	.046
Time until first negative fluid balance (d)	2.0 (1-4)	2.5 (2-3)	.027
Time until sternal closure (d)	2.5 (0-6)	4.0 (0-6)	.14
Time until first extubation (d)	6.0 (3-17)	6.0 (4-13)	.38
In-hospital death* (No.)	0	0	>.999
Extracorporeal membrane oxygenation (No.)	0	2 (10%)	.22

Each subcomponent of the clinical score is also presented. Results are presented as median with range as appropriate. *One patient randomly assigned to the placebo group died at home 5 weeks after hospital discharge; 1 patient was randomly assigned to the placebo group but excluded post hoc before initiation of study drug and died in the hospital.

postoperative hours but were similar between treatment groups immediately before and after CPB and at 7 and 14 postoperative days (Figure 1, *A* and *B*). Levels of total and free T_4, thyroid-stimulating hormone, and T_3 resin uptake did not differ between the two groups at any time before or after surgery (data not shown).

Composite clinical outcome score (Table 1) was a primary end point. The median scores were 2.0 (range 0-4) in the T_3 group and 2.0 (range 0-7) in the placebo group, a significant difference ($P = .046$) that arose from a difference in the distribution of values; the only patients with a score greater than 4 were in the placebo group (Table 3). The median time until a negative fluid balance was first achieved was lower in the T_3 group, at 2.0 days (range 1-4 days), than in the placebo group (2.5 days, range 2-3 days, $P = .027$). After controlling for duration of circulatory arrest, the magnitude of this effect did not change ($P = .05$). Time until sternal closure and duration of mechanical ventilation were not significantly different between the treatment groups.

Although our trial was designed with CI as one of the two primary end points, its measurement was not feasible in 9 patients in the T_3 group and 5 patients in the placebo group because of unreliable Co_2 data (n = 10) or lack of a superior vena cava blood sample at 48 postoperative hours (n = 4). Among patients in whom CI could be measured, the mean values at 48 postoperative hours were 2.11 ± 0.64 L/min · m^2 in the T_3 group and 2.05 ± 0.72 L/min · m^2 in the placebo group ($P = .81$). The mean arterial pH was similar between the T_3 and placebo groups when CI was measured (7.44 ± 0.05 and 7.43 ± 0.04, respectively, $P = .64$), as was the mean $Paco_2$ (49.4 ± 6.30 mm Hg and 47.3 ± 7.13 mm Hg, respectively, $P = .33$).

Systolic blood pressure was significantly higher in the T_3 group ($P < .001$; Figure 2, *A*), as was mean blood pressure ($P = .02$; Figure 2, *B*). However, heart rate and diastolic blood pressure were not different between treatment groups (data not shown).

Do_2 values at 48 postoperative hours were 342 ± 109 mL/(min · m^2) in the T_3 group and 321 ± 108 mL/

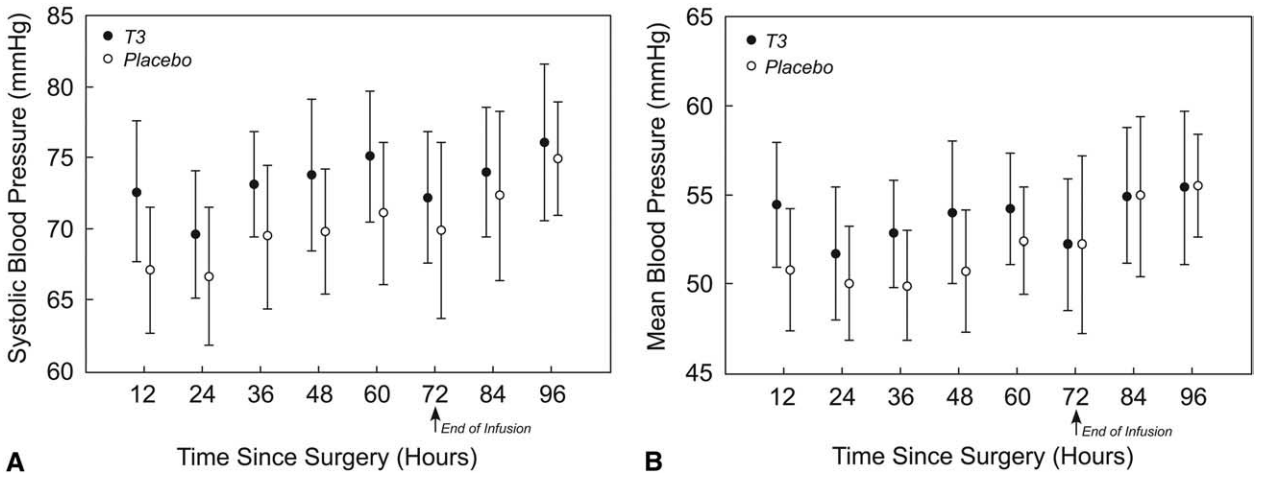

Figure 2. Systolic blood pressure (A) was higher in the T_3 group ($P < .001$) during the early postoperative period, as was mean blood pressure (B) ($P = .02$). *Error bars* represent 95% confidence intervals.

($\min \cdot m^2$) in the placebo group ($P = .62$). Co_2 values, measured at the same time, were 110 ± 22 mL/($\min \cdot m^2$) in the T_3 group and 108 ± 24 mL/($\min \cdot m^2$) in the placebo group ($P = .82$). The Do_2/Co_2 ratios were also equivalent at 3.20 ± 0.91 in the T_3 group and 3.22 ± 1.31 in the placebo group ($P = .96$).

The mean 5-day inotrope scores were 63.2 ± 32.4 mg/kg in the T_3 group and 69.1 ± 32.3 mg/kg in the placebo group ($P = .56$). Mean inotrope scores at 12, 24, and 48 hours were also similar between treatment groups (data not shown). The median ICU stays were 7.5 days (range 4-47 days) in the T_3 group and 8.5 days (range 5-96 days) in the placebo group ($P = .52$). The median total hospital stays were 16.5 days (range 8-95 days) in the T_3 group and 18 days (range 9-112 days) in the placebo group ($P = .59$). Median times until enteral feeding was started were 4 days (range 2-7 days) in the T_3 group and 5 days (range 2-7 days) in the placebo group ($P = .35$). There were no differences in serum lactate, ionized calcium, or cortisol between groups either before or after the operation (data not shown).

The incidence of serious adverse events, including cardiac arrest, renal failure, and infectious complications, did not differ between treatment groups. No serious adverse events were attributed directly to the administration of study medication.

Discussion

In a population of neonates undergoing high-risk open heart surgery, we found that postoperative treatment with T_3 for 72 hours was associated with significantly better clinical outcome scores than was treatment with placebo, with the difference attributable to more rapid achievement of a negative fluid balance in the T_3 group. Systolic and mean blood pressures were higher in T_3-treated patients. For technical reasons, we were unable to measure CI in a third of the patients; however, among those in whom CI was measured, we found no difference between treatment groups. T_3 supplementation did not increase Co_2 at the expense of Do_2 and was not associated with important adverse events. To our knowledge, this study represents the largest prospective clinical trial published to date of T_3 supplementation in neonates after cardiac surgery.

Previous studies on T_3 supplementation in pediatric patients have suggested that its administration may benefit recovery after cardiac surgery. Mainwaring and colleagues[18] gave two bolus doses of T_3 after the Fontan procedure to 10 children aged 19 to 42 months. Relative to a historical control group, the T_3 group had a significantly shorter period of mechanical ventilation. Bettendorf and associates[10] randomly allocated 40 children undergoing a wide variety of cardiac procedures to receive bolus dosing of T_3 or placebo. Patients in the T_3 group had lower Therapeutic Intervention Scoring System (TISS) scores than did those in the placebo arm. Cardiac output was higher in the treatment group 24 hours after surgery, as measured by Doppler echocardiography. Chowdhury and coworkers[9] randomly assigned 28 children aged 0 to 18 years to a 5-day continuous infusion of T_3 (0.05-0.15 μg/[kg $\cdot$ h]) or placebo. Among the subset of neonates (n = 9), the T_3 group had lower TISS scores and lower inotrope requirements. The T_3 group also had a trend toward higher mixed venous oxygen saturations, fewer days of mechanical ventilation, and a shorter postoperative stay.

Our findings may differ from those of other authors on the basis of several factors. We used different primary outcome measures (a composite clinical outcome score and CI determined by real-time gas-exchange measurement of Co_2), and we measured CI at 48 rather than 24 postoperative hours. In addition, we administered a continuous infusion of T_3 rather than bolus dosing, without adjustment of the infusion rate according to T_3 levels. Only one previous pediatric study has used a continuous infusion,[9] and those investigators adjusted the infusion rate to maintain serum total T_3 levels within a target range; the doses used were also as great as 3 times the dose we used. However, we achieved T_3 levels in the treatment group that were within normal range and were significantly higher than in the placebo group.

The more rapid achievement of a negative fluid balance in children treated with T_3 may have several explanations. Thyroid hormones are important for the normal function of all organs, and low free T_3 levels in the placebo group may have impaired intrinsic renal function. Alternatively, higher systolic blood pressures in the T_3 group may have contributed to improved renal perfusion and glomerular filtration. The difference in circulatory arrest times between the T_3 and placebo groups, however, does not explain the difference in time to negative fluid balance.

Limitations

The clinical outcome score used has not been previously validated. Nonetheless, our score discriminated patients receiving T_3 infusion from those receiving placebo. The inability to measure CI in an important percentage (33%) of subjects was also a limitation. Although free from the assumptions inherent in measuring CI by Doppler echocardiography,[19] direct measurement of Co_2 by real-time gas exchange requires a sedated, mechanically ventilated patient who has not had a change in hemodynamic or respiratory status for at least 1 hour. Furthermore, "true" mixed venous oxygen saturation could not be measured in patients undergoing the Norwood procedure. We approximated this variable by measuring $Ssvco_2$. This value is influenced by cerebral blood flow, which in turn is influenced not only by cardiac output but also by serum pH and $Paco_2$.[20] However, arterial pH and $Paco_2$ did not differ between the T_3 and

placebo groups at the time of CI determination. Finally, transcutaneous absorption of iodine, well described in infants,[21,22] is a potential confounder of our study findings. Although all patients were exposed to iodine for skin antisepsis during the perioperative period, no attempt was made to quantify either the volume of iodine used or the duration of exposure on a per patient basis.

We observed a shorter ICU stay and total hospitalization in the T_3 group. Although these findings were not statistically significant, our study lacked sufficient power to demonstrate a significant difference in these end points. A larger, multicenter study might be able to find an impact of T_3 supplementation on the durations of ICU and hospital stay. The potential benefit of T_3 supplementation in T_3-deficient patients who are further out from surgery and yet remain critically ill is also unknown.

In summary, we found that T_3 supplementation in neonates after high-risk cardiac surgery was safe and resulted in favorable composite clinical outcome scores in the early postoperative period as a result of more rapid achievement of a negative fluid balance. Co_2 was not increased at the expense of Do_2. Systolic and mean blood pressures were higher in patients who received T_3. However, CI measured at 48 postoperative hours was not influenced by T_3 infusion. The routine use of T_3 in neonates after cardiac surgery is not supported by our findings; however, patients with oliguria and marginal blood pressure may benefit. Larger, multicenter studies should examine the role of T_3 repletion in children undergoing other congenital heart procedures and the impact of T_3 supplementation in patients with prolonged critical illness after neonatal cardiac surgery.

We acknowledge the members of the Data Safety and Monitoring Board: Lynn Mahony, MD (chair), Children's Medical Center of Dallas; Henry Feldman, PhD, Children's Hospital Boston; Thomas P. Foley, Jr, MD, Children's Hospital of Pittsburgh; Thomas Kulik, MD, C.S. Mott Children's Hospital; Lainie Ross, MD, PhD, MacLean Center of Clinical Medical Ethics; and James S. Tweddell, MD, Children's Hospital of Wisconsin. We also acknowledge Lida Kyn for computer programming; Donna Donati and Donna Duva for data entry; nurses of the Cardiac Intensive Care Unit, Children's Hospital Boston, for managing study drug infusion and blood work as needed; The Glaser Pediatric Research Network, which provided salary support for Andrew Mackie; King Pharmaceuticals (Cary, NC), for providing study drug; and the General Clinical Research Center, Children's Hospital Boston, for funding all laboratory investigations.

CHD

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